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Travelers' Diarrhea

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On the average, one-fourth of North Americans visiting developing countries experience a self-limited diarrheal illness that interferes with holiday or business activities. Recent work suggests that these episodes are caused by a small inoculum of enteropathogenic Escherichia coli which are common in the country visited and rare in the country of origin. Neither antimicrobial treatment nor anti-diarrheal agents have proven benefit once the illness has begun. Despite its frequent use, iodochlorhydroxyquin has not been shown in double blind studies to be effective as a preventive agent, and may be dangerous. The status of furazolidone for prevention of tourist diarrhea is questionable. Both neomycin sulfate and phythalylsulfathiazole have demonstrated efficacy as chemoprophylactics in Mexico. However, their use should be restricted to limited types of travel and travelers.

General admonitions concerning avoidance of certain ingestibles are recommended; despite questionable value in preventing travelers' diarrhea such precautions may prevent more serious gastrointestinal illness.

MORE THAN four and half million American citizens left the United States in 1970 for foreign countries, excluding trips to Europe and border crossings, according to the U.S. Travel Service. Last year nearly 25,000,000 border crossings were made into Tiajuana alone. Travel to countries other than Canada and Northern Europe is associated with a number of medical hazards, the most common if least serious of which is travelers' diarrhea. Athough traditionally the traveler experiencing this syndrome was better informed as to its nature than the average physician, a number of recent investigations have at last shed some scientific light on the cause, characteristics and possible prevention of this illness.

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Epidemiology

The frequency of travelers' diarrhea varies with the age of the traveler, the country visited, and the country of origin of the traveler. Both sexes are equally susceptible, although the risk appears to

decrease with age.[1] The lowest and the highest reported incidences were derived from retrospective studies; 7.5 percent of air travelers returning from Hawaii to the United States and 71 percent of American students returning from the Mediterranean by ship reported tourist diarrhea.[2,3] In prospective and retrospective studies of North Americans visiting Mexico City, one-fourth to one-third had tourist diarrhea.[1,4,5] Travelers' diarrhea is most common in persons from northern industrialized nations visting warmer and less sanitated countries. Thus, United Nations observers from Europe and North America experienced significantly more diarrhea when dispersed throughout Lebanon than did those observers originating from Asia and South America.[6] Similarly, only 8 percent of 163 travelers from tropical countries visiting a medical congress in Teheran had diarrhea, against 41 percent of 230 from countries with more temperate climates. These observations suggest that immunity plays a role in travelers' diarrhea and supports the concept that the disease is caused by an infectious agent. Two-thirds of affected persons become ill within the first two weeks of travel, but diarrhea is rare in the first three days;[2] this apparent incubation period also makes infection a probable cause.

Signs and Symptoms

The symptoms are remarkably similar whereever travelers' diarrhea is acquired. Non-bloody diarrhea, with or without nausea, vomiting, abdominal pain and malaise are typical. Although not generally considered to be a febrile illness, subjective fever complicates three-fourths of cases occurring in Mexico, and chills occur in half.[2] Severity varies from a few diarrheal stools which do not interfere with activity to an illness of longer than three days. However, the latter occurs in less than 15 percent of cases.[2] Nevertheless, one-third of affected travelers are sufficiently prostrated or "toilet-bound" to be confined to quarters for one to three days.[2] Patients generally appear tired and weak, but physical examination reveals little except low-grade fever and occasional tenderness over the transverse colon.

Cause

Patients in whom symptoms, physical findings or duration of illness do not fit this pattern are arbitrarily excluded from a diagnosis of travelers' diarrhea, and may have salmonellosis, shigellosis, giardiasis or amebiasis. These pathogens, however, are not responsible for more than 5 to 15 percent of enteric illness in travelers, the vast majority of whom have no shigella, salmonella, parasites or viruses recovered from stool.[3,8-11] The exclusion of viral infection as a cause is always suspect, in that available culture techniques may not permit recovery of all agents. Nevertheless, the apparent preventive effect of antimicrobials (vide infra) supports suspicion of bacterial rather than viral infection. Current work suggests that this disease is caused by enteropathogenic Escherischia coli; earlier failures to demonstrate this association were caused by limiting the search to recognized infantile pathogenic serotypes.[8] Recently a new serotype of E. coli with antigenic structure 0148: H28 was demonstrated in about half of 35 acute cases of diarrhea occurring in British soldiers during their first 14 days after arrival in Aden.[11] This serotype was never isolated from healthy subjects. Pathogenicity of this serotype for adults was demonstrated when a technician working in England, where the serotype is not found, acquired a laboratory infection and had severe diarrhea; E. coli 0148:H28 was recovered in pure culture from the stool. This exciting work suggests that in "any investigation (of travelers' diarrhea) E. coli strains must be fully serotyped and workers must be prepared to identify new serotypes and determine their relation to diarrhea."[11] Although it seems likely that a variety of serotypes will ultimately be found to be responsible for travelers' diarrhea in different parts of the world, and indeed in the same place at different times, the lower attack rates in travelers from other tropical or semi-tropical climates could be interpreted as evidence for immunity to like organisms.

Treatment

Therapy for this self-limited illness is without demonstrated benefit. Since few patients are ill for more than three days, success can be attributed to almost any medication taken. Antimicrobials may cause untoward reactions or mask more serious disease and cannot be recommended for tourist diarrhea of less than three days' duration. Persons ill for longer periods deserve microscopic and cultural examination of stool rather than empirical use of antibiotics. The value of non-specific anti-diarrheal agents designed to reduce the frequency of bowel movements is similarly unproven, although anecdotal

experience suggests that they may relieve the debilitating effects of fluid and electrolyte loss. There is, however, a theoretical reason why such agents are undesirable in that unchecked diarrhea may serve to cleanse the bowel of the infecting agent. It has been shown that enterotoxin-producing E. coli, like 0148:H28, and the enterotoxin itself are not firmly bound to the bowel mucosa and can be washed out.[12,13]

Prevention

Many travelers—up to 40 percent in one retrospective study of air travelers to Mexico—self-medicate themselves with prescription or proprietary agents in hopes of either preventing or minimizing the severity of tourist diarrhea.[1] Several controlled studies have been conducted in an effort to evaluate the prophylactic value of specific agents against travelers' diarrhea (Table 1).

Iodochlorhydroxyquin (Entero-vioform®, Vioform,® clioquinol) has probably been the most widely used.[7] The use of this agent may have begun with the mistaken belief that tourist diarrhea was amebic in origin and belief in it perpetuated by the self-limited nature of the illness. The fact is that double blind randomized study of North American students in Mexico City showed the incidence of diarrhea to be significantly greater in travelers taking iodochlorhydroxyquin than in those taking placebo.[4] In contrast, Richards reported a significant reduction of diarrhea in athletes traveling mainly to European countries, when iodochlorhydroxyquin was taken prophylactically.[14,15] These studies are not entirely satisfactory in that they were neither double blind nor randomized. In addition the results do not distinguish very mild gastrointestinal upset from more severe diarrhea, and the reduction could be attributed in part to the lessening of bowel gas through use of this drug.[16] In addition, the safety of iodochlorhydroxyquin is questionable. Scandinavian tourists visiting Mediterranean countries who regularly used oxyquinolines prophylactically acquired salmonellosis significantly more often than tourists not taking this drug.[17] Further, Japanese studies strongly suggest that a severe and not necessarily reversable neurologic syndrome, subacute myelo-optic neuropathy (SMON), is related directly or indirectly to the use of clioquinol: 85 percent of persons in whom SMON developed had taken clioquinol, the risk was dose related, and the syndrome nearly disappeared following discontinuance of this drug.[18] Unfortunately, the traditional use of this agent and its non-prescription status in many countries, suggest that iodochlorhydroxyquin will continue to be used for tourist diarrhea despite its doubtful efficacy and possible dangers.

A double blind study of Royal Air Force men visiting countries east of the Mediterranean showed furazolidone to be effective as a chemoprophylactic agent against tourist diarrhea.[19] In Mexico, diarrhea developed in two of seven teachers from New York who were taking no drug while none of ten teachers taking 400 mg of furazolidone daily for two weeks had the disease, although seven complained of continual nausea.[2] In an uncontrolled study, eight of eleven travelers to Mexico developed diarrhea despite furazolidone, 200 mg daily.[2] The status of this drug for the pro-

TABLE 1.—*Controlled Studies of Chemoprophylaxis for Travelers' Diarrhea*

Drug	*Diarrhea With Drug*	*Diarrhea With Placebo*	*Study Population*
Iodochlorhydroxyquin 250 mg bid, tid or qid (3 studies combined)...	16 of 499 (3.21%)	42 of 279 (15.5%)	Mainly male athletes, world travel[14]
Iodochlorhydroxyquin 375 mg bid.	81 of 210 (38.6 %) *34 of 210 (16.2 %)**	68 of 202 (33.6%) *22 of 202 (10.9%)**	U.S. students in Mexico[4]
Neomycin sulfate 375 or 500 mg bid (2 studies combined).....	62 of 335 (18.5 %) *20 of 335 (5.97%)*	108 of 370 (29.2%) *51 of 370 (13.8%)*	U.S. students in Mexico[4,5]
Furazolidone 100 or 200 mg qd..	*28 of 407 (6.88%)*	*57 of 201 (28.4%)*	Royal Air Force males east of Mediterranean[19]
Phthalylsulfathiazole 1 gm bid...	20 of 168 (11.9 %) *11 of 168 (6.55%)*	40 of 168 (23.8%) *29 of 168 (17.3%)*	U.S. students in Mexico[5]

NOTE: Data in roman letters refers to all degrees of diarrheal illness. Data in italics refers to diarrhea of severity to interfere with daily activity or to require medical treatment.

*All differences are statistically significant (t test) except this value.

phylaxis of tourist diarrhea, therefore, remains in doubt.

Both neomycin sulfate and phthalsulfathiazole have been shown in good drug trials to reduce the risk of tourist diarrhea significantly in Mexico.[5] It remains to be seen whether these drugs would be beneficial in other parts of the world. The only other study (of British Overseas Airways Corporation personnel and their families going abroad who were said to have found no protection in a neomycin-sulfonamide combination) is unsatisfactory in that specific data are not presented.[20]

Physicians recommending chemoprophylaxis should consider the risk of drug, the risk of turista, and the duration and purpose of the visit. Persons planning a short visit to Latin America, when the purpose of the trip would be seriously impeded by the development of tourist diarrhea, and when there is no medical contraindication to neomycin or phthasulfathiazole, can be offered chemoprophylaxis. Persons traveling for more than three weeks are rarely if ever candidates for prolonged chemoprophylaxis.

No drug is wholly effective in preventing travelers' diarrhea. Therefore, whether or not drug prophylaxis is used, the traveler should be advised about general precautions. These include the avoidance of local water supplies, including ice. Safe bottled liquids are those that are sealed (more than one traveler has returned to the hotel to find the maid refilling the "bottled water" from the tap). It is also recommended that travelers avoid fresh fruit and vegetables unless they are cooked or can be peeled. Many physicians advise travelers to avoid spicy or unusual native dishes and excessive fatigue and alcohol, although few heed these admonitions. All these recommendations make sense, but there is little information to support their efficacy. A study by the Center for Disease Control of persons attending a medical congress in Mexico City showed no difference in the attack rates of diarrhea in those who ate and drank without precautions than in those who drank only bottled liquids and avoided salads and the like.[21] This information is compatible with the hypothesis that ubiquitous E. coli of serotypes foreign to the traveler are responsible for the disease, and that only a small inoculum is required to produce illness. Nevertheless physicians should continue to make the same general recommendations to travelers, in the hope that such measures will at least reduce the risk of acquiring more serious gastrointestinal infections.

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